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First total syntheses of the 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines annoretine and litebamine

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Abstract—We describe here the first total synthesis of the two natural 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines, annoretine and litebamine, from [2-(2-styrylphenyl)ethyl]methylcarbamic acid ethyl esters. The key steps were the Bischler–Napieralski cyclization to form the isoquinoline unit and photocyclization of the resulting 2-methyl-5-styryl-3,4-dihydro-2*H*-isoquinolin-1-ones to 2-methyl-3,4-dihydro-2*H*-naphtho[2,1-*f*]isoquinolin-1-ones.

Isoquinolines have received considerable attention because derivatives of the isoquinoline ring system have been identified as the major structural motifs in a wide range of natural compounds of chemical and biological interest.[1] However, surprisingly, naphtho[2,1-*f*]isoquinolines (2-aza-chrysenes) have received very little attention[2] and the corresponding tetrahydro derivatives (1,2,3,4-tetrahydro-naphtho[2,1-*f*]isoquinolines) have not been considered prior to the recent report concerning the isolation of the only two natural members of this family—litebamine (**1b**)[3] and annoretine (**1a**).[4]

Litebamine was the first phenanthrenic alkaloid isolated from *Litsea cubeba* and its activity as a platelet anti-aggregant[5] and against acetyl choline esterase[6] have been described. Subsequent partial syntheses of litebamine from the aporphine boldine led to the hypothesis of biogenetic degradation of aporphines to 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines.[7] Annoretine was isolated from the leaves of *Annona montana* and it possesses significant cytotoxic activity against different human cell cultures such as KB, P-388, A-549 and HT-29.[4] No other partial or total synthesis of these new isoquinoline alkaloids has been reported to date.

In relation to a previous paper[8] on this journal and given our previous exploratory work on the synthesis of naphtho[2,1-*f*]-isoquinolines,[9] we describe here the first total synthesis of annoretine[10] and litebamine, an exercise that allowed us to corroborate structures proposed for these natural compounds and to establish a promising method for the large scale preparation of these and other 1,2,3,4-tetrahydro-naphtho[2,1-*f*]isoquinolines for chemical and biological studies.

Our synthetic strategy was based on a sequential construction of rings C and A, starting from styrylphenylethyl-urethanes **3** (Scheme 1); these latter compounds contain a convenient stilbene-like unit for construction of the ring system of phenanthrenes **2** and so final transformation of these intermediates into the target compounds **1** should be achieved by Bischler–Napieralski cyclization, followed by demethylation and reduction. Alternatively, ring A could be constructed first, giving 5-styrylisoquinolines **4**,[7c] which could then be transformed into naphthoisoquinolines **1** by electrocyclic cyclization followed by demethylation and reduction.

We first studied the preparation of annoretine (**1a**) starting from *o*-styrylphenylethylurethane **3a**, which was prepared by Heck[11] coupling of the appropriate halobenzene **5c** to styrene (**6a**) (Scheme 2). A solution of homoveratrylamine (**5a**), ethyl chloroformate and Et_3N was stirred at rt for 16 h to afford the *N*-carbethoxy derivative **5b** in 93% yield. This compound was subsequently transformed into iodobenzene derivative **5c** in 99% yield after treatment with IPy_2BF_4[12] and CF_3SO_3H. When a deoxygenated solution of **5c**, styrene (**6a**), triethylamine, triphenylphosphine and palladium acetate was heated at 100°C in a sealed tube for 24 h, the

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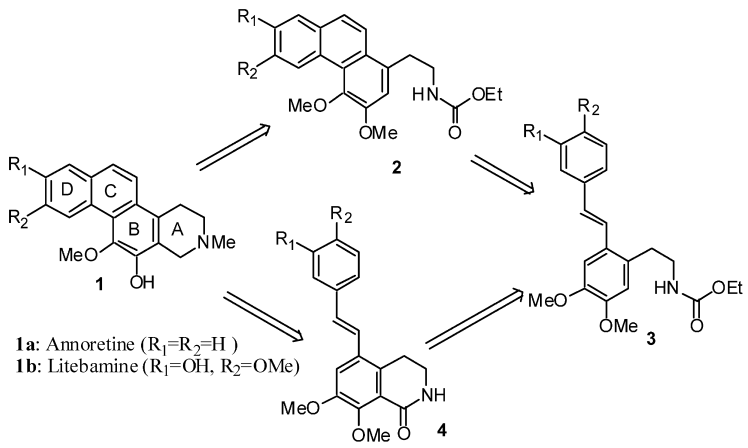


Scheme 1.

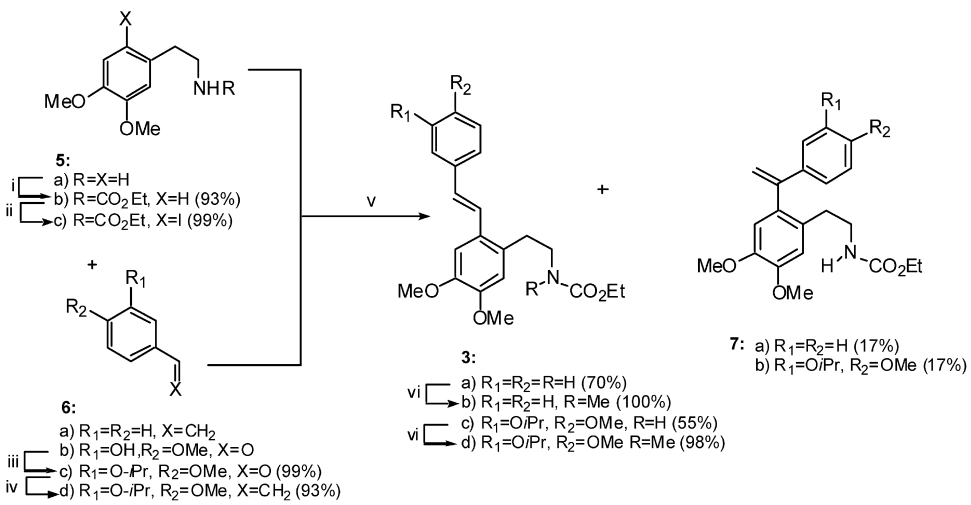
desired disubstituted *o*-styrylphenylethylurethane **3a** was obtained in 70% yield together with 17% of the corresponding α-coupled alkene **7a**. The mass spectrum of **3a** confirmed the expected molecular weight (*m*/*z*=355) and the *E* configuration of the stilbene double bond was easily established from its ^{1}H NMR spectrum, which showed a doublet at 6.90 ppm (1H, *J*=16.1 Hz) due to one proton on the double bond. The doublet corresponding to the other vinylic proton was located in one of the complex signals due to aromatic protons.

We next studied the photochemically induced electrocyclic cyclization[13] of styrylphenylethylurethane **3a** in order to obtain the corresponding phenanthrenylethylurethane **2a** (Scheme 1). However, irradiation of **3a** with a 450 W Hanovia medium-pressure lamp equipped with a Pyrex filter did not give **2a**, but did produce phenanthrene **12** as a consequence of the removal of the ethylurethane chain of **3a** (Scheme 3).

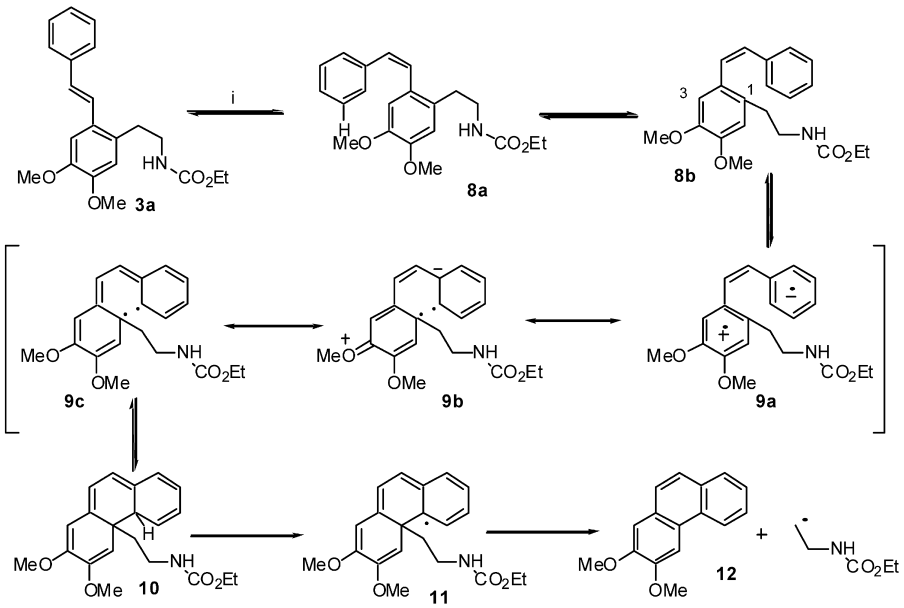
The positions of the methoxy substituents on the resulting phenanthrene **12** clearly show that this compound results from the cyclization of *cis*-stilbene **8b** through position C(1) instead of the desired cyclization through position C(3). A plausible mechanism for the formation of phenanthrene **12** involves electron transfer from the disubstituted aromatic ring to the unsubstituted ring of **8b**, which leads to a cation-radical/anion-radical (**9a**) that can also be described by resonance structures **9b** and **9c**. The latter species is a stabilized diradical, the presence of which could explain the formation of dihydrophenanthrene **10**. Oxidation of this compound by iodine to **11**, followed by the concomitant expulsion of the alkyl chain, allows an aromatization process to occur and give compound **12**.

This unexpected result led us to explore the aforementioned alternative synthesis of annoretine (**1a**) from **3a** via 5-styrylisoquinoline **4a** (Scheme 1). After an initial unsuccessful attempt to promote Bischler–Napieralski cyclization of **3a** to **4a** with Tf_2O (Scheme 4),[14] compound **3a** was converted into its *N*-methyl derivative **3b** (Scheme 3) and this was subjected to the above Bichler–Napieralski cyclization conditions. This reaction readily furnished the expected 5-styrylisoquinolinone **4b** in 77% yield.

In the next step of our programme the photolysis of styrylisoquinoline **4b** was studied (Scheme 4).[9b] Irradiation of this compound under the same conditions as for **3a** gave



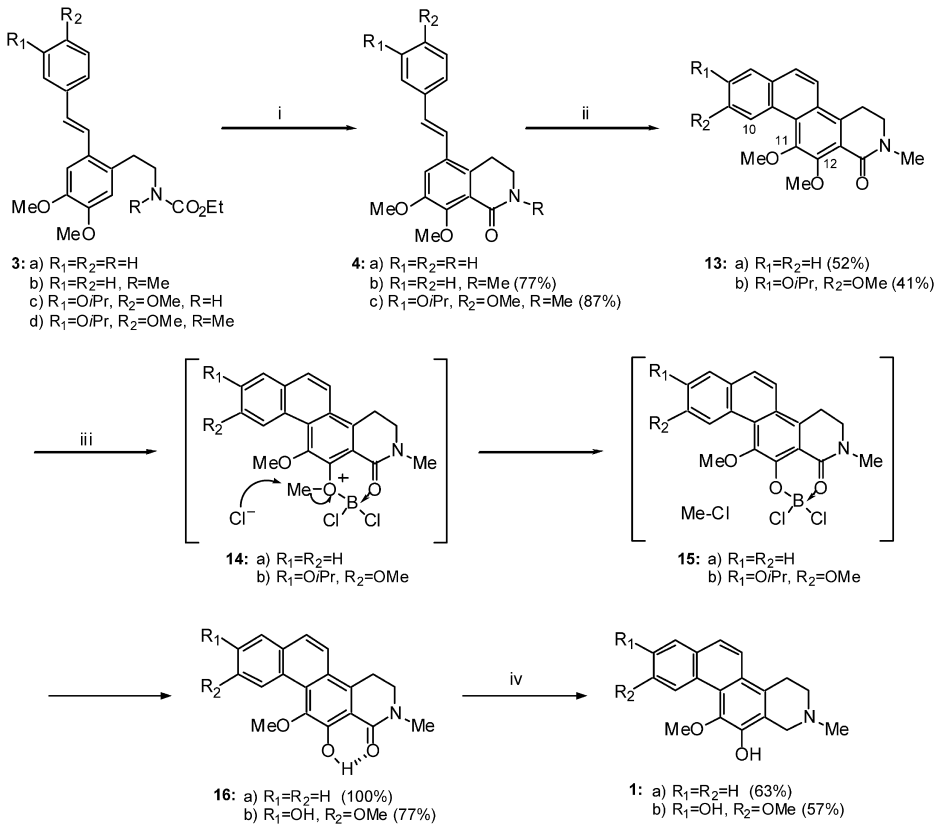
Scheme 2. (i) Et_3N, $ClCO_2Et$, dry CH_2Cl_2, argon, 0°C–>rt, 16 h. (ii) CF_3CO_2H, IPy_2BF_4, dry CH_2Cl_2, argon, 0°C, 30 min. (iii) K_2CO_3, dry DMF, 2-bromopropane, rt, 48 h. (iv) *n*-BuLi, $CH_2{=}PPh_3^+Br^-$, THF, argon, 0°C–>rt, 4 h. (v) $Pd(OAc)_2$, Ph_3P, Et_3N, dry MeCN, argon, 80°C, 24 h. (vi) (a) NaH, dry THF, argon, rt, 30 min; MeI, argon, rt, 3 h.



Scheme 3. (i) UV light, I_2, Et_2O/CH_2Cl_2, rt, 5 h.

the expected naphthoisoquinolinone **13a** with the tetracyclic framework of annoretine—which was identified from its analytical and spectroscopic data. The mass spectrum of this compound confirmed the molecular mass (M^+, m/z=321), two units less than the starting material. In addition, the ^1H NMR spectrum showed signals for a total of six aromatic protons, including a multiplet for a proton at 9.67–9.70 ppm due to the hydrogen at C(10), which is highly deshielded due to steric interaction with the methoxy substituent at position C(11).

Transformation of naphthoisoquinolinone **13a** into annoretine was accomplished in a two-step sequence starting with treatment of **13a** with BCl_3 at rt during 15 min,[15] which led to compound **16a** as a result of regiospecific demethylation of the methoxy substituent at C(12). Clear evidence for this process was provided by spectroscopic data—particularly the ^1H NMR spectrum, which showed a highly deshielded singlet for one proton at 13.05 ppm. This signal was assigned to the proton of the hydroxy substituent.



Scheme 4. (i) Tf_2O, DMAP, dry CH_2Cl_2, 0°C–>rt, 21 h. (ii) UV light, I_2, Et_2O, rt, 3 h. (iii) BCl_3, CH_2Cl_2, rt, 15 min. (iv) $LiAlH_4$, THF, 0°C–>rt, 5 h.

The marked downfield chemical shift for this proton, due to its interaction with the carbonyl group, allowed us to establish that demethylation had occurred at the desired position. This conclusion was further supported by HMQC and HMBC experiments, which show a correlation between the OH proton and carbon atoms C(12a) and C(11), together with a correlation between the methoxy substituent and the carbon at C(11) (Fig. 1).

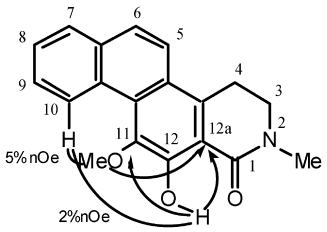


Figure 1. Important $^{1}H-^{13}C$ couplings observed in the HMQC and HMBC experiments of compound **16a**.

These correlations clearly indicate that the hydroxy substituent is located between the carbonyl group and the methoxy substituent. Furthermore, the main conclusion of the nOe experiments is that irradiation of the proton at C-10 gives a 5% nOe with the methoxy group and a 2% nOe with the proton of the hydroxy group.

Selective demethylation of the methoxy substituent at C(12) can be explained as being the result of the initial interaction between naphthoisoquinolinone **13a** and BCl_3, which leads to a coordination complex **14** in which the boron atom is coordinated with oxygen atoms of the carbonyl and methoxy groups; attack on such a complex by a chloride ion gives a second boron complex **15**, hydrolysis of which furnished the resulting phenolic naphthoisoquinoline **16a**.[16]

Finally, reduction of compound **16a** with $LiAlH_4$ provided annoretine (**1a**) in 63% yield. The structure of this compound was unequivocally confirmed by an X-ray diffraction experiment (Fig. 2).[17]

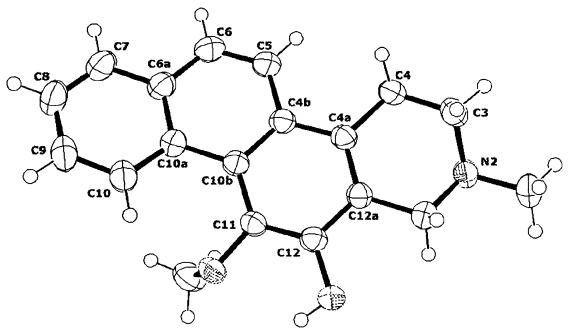


Figure 2. ORTEP drawing of annoretine (**1a**).

We next decided to apply the above strategy to the synthesis of litebamine (**1b**). This tetrasubstituted 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline possesses two hydroxy groups (at positions C(8) and C(12)) and we envisaged that only the latter hydroxy substituent could be generated by a selective demethylation similar to that used for annoretine (**1a**). We therefore decided to start with styrene **6d** (Scheme 2), with a hydroxy group masked as the isopropoxy derivative, a relatively uncommon protecting group for phenols that is able to resist the basic, acidic and photochemical conditions required in this synthesis. The protecting group can be removed with boron trichloride.[18]

Treatment of isovanillin (**6b**) with isopropyl bromide under basic conditions gave an excellent yield of the corresponding benzaldehyde **6c**, which was then converted into the desired styrene **6d** in 93% yield by means of a Wittig reaction involving treatment of **6c** with Ph_3PCH_3Br and *n*-BuLi in THF at rt for 4 h.[19] Salient signals in the ^{1}H NMR spectrum of this compound are two doublet of doublets at 5.58 ppm (J=17.6, 0.9 Hz) and 6.61 ppm (J=17.6, 10.9 Hz), together with a doublet at 5.11 ppm, all due to the protons of the double bond. Subsequent Heck coupling of iodophenylethylurethane **5c** to styrene **6d** under the conditions used for the preparation of **3a** allowed us to obtain a 3:1 mixture of compounds **3c** and **7b**, the expected compounds corresponding to the β and α coupling, respectively (global yield 72%). The ^{1}H NMR spectrum of **3c** contained complex groups of signals corresponding to the five aromatic protons and the protons of the double bond. In addition, signals for the aliphatic protons were observed, including a broad singlet at 4.87 ppm due to the proton of the NH group. Stilbene **3c** was subsequently reacted with methyl iodide and the resulting *N*-methyl derivative **3d** was then subjected to the previously described Bischler–Napieralski cyclization conditions to give the expected styrylisoquinolinone **4c** in 87% yield. Photolysis of this compound under the conditions described for **4b** gave a 41% yield of naphthoisoquinolinone **13b**. This compound was easily identified from its analytical and spectroscopic data—particularly from its ^{1}H NMR spectrum, which showed signals for a total of four aromatic protons (two fewer than the starting material) including the expected singlet at 9.26 ppm corresponding to the highly deshielded proton at C(10).

The next step in the planned route involved the selective demethylation of the methoxy group at C-12 and removal of the isopropyl group at C-8. These transformations were achieved in a single step when compound **13b** was reacted with BCl_3 in dichloromethane for 15 min, as described above. Finally, litebamine (**1b**) was obtained in 57% yield by reduction of **16b** with $LiAlH_4$ and its structure was unequivocally confirmed by X-ray diffraction (Fig. 3).[20]

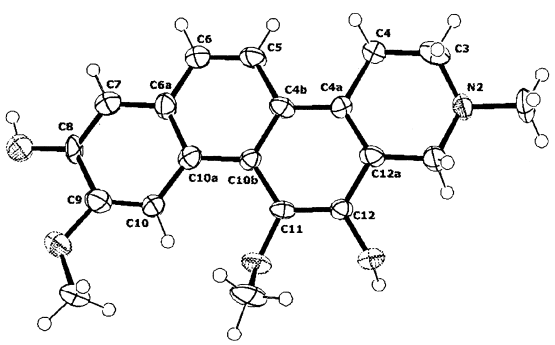


Figure 3. ORTEP drawing of litebamine (**1b**).

In summary, we have developed a total synthesis of 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines that has allowed us to carry out the first total synthesis of annoretine and litebamine. We would like to highlight the contribution that this study represents in the chemistry of 5-styrylisoquinolines, which have hitherto received very little attention.

Work is now in progress to prepare a range of non-natural 1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolines for chemical and biological studies.

1. Experimental

1.1. General

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra, unless otherwise specified, were recorded on a Bruker WM-250 apparatus using deuterochloroform solutions containing tetramethylsilane as internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and dichloromethane/methanol mixtures as eluant; the tlc spots were visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified according to Ref. 21. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

1.1.1. [2-(3,4-Dimethoxyphenyl)ethyl]carbamic acid ethyl ester (5b). Triethylamine (14.5 mL, 110 mmol) and then ethyl chloroformate (7.2 mL, 75.038 mmol) were added dropwise under argon to a solution of homoveratrylamine (**5a**) (4 g, 22.070 mmol) in dry dichloromethane (25 mL) at 0°C. The mixture was stirred for 16 h under argon at rt. The reaction mixture was concentrated in vacuo, the residue was suspended in water (25 mL) and the suspension was extracted with dichloromethane (3×20 mL). The combined organic extracts were washed with water, dried, filtered and concentrated in vacuo. The resulting oily residue was purified by column chromatography (eluant: 1:1 ethyl acetate/hexane) to give compound **5b** (5.198 g, 93% yield) as a white solid. Mp 53–55°C (methanol). IR (ν, cm^{-1}, NaCl): 3304 (–NH), 1683 (CO). ^1H NMR (δ, ppm): 6.80–6.69 (m, 3H, 3×ArH), 5.27 (bs, 1H, –NH), 4.08 (q, J=7.0 Hz, 2H, $-OCH_2CH_3$), 3.84 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 3.42–3.34 (m, 2H, $-CH_2-$), 2.77–2.71 (m, 2H, $-CH_2-$), 1.20 (t, J=7.0 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 156.19 (CO); 148.38 ($ArOCH_3$); 147.03 ($ArOCH_3$); 130.98 (C); 120.13 (ArH); 111.45 (ArH); 110.83 (ArH); 59.98 ($-OCH_2CH_3$); 55.26 ($-OCH_3$); 55.17 ($-OCH_3$); 41.76 ($-CH_2-$); 35.16 ($-CH_2-$); 14.09 ($-OCH_2CH_3$). MS (*m*/*z*, %): 253 (M^+, 14), 151 (100). HRMS (CI): $C_{13}H_{20}NO_4$ (M^++H), calcd 254.1314; found 254.1321.

1.1.2. [2-(2-Iodo-4,5-dimethoxyphenyl)ethyl]carbamic acid ethyl ester (5c). Trifluoromethanesulfonic acid (1.15 mL, 12.900 mmol) was added dropwise under argon to a stirred solution of *N*-carbethoxy derivative **5b** (1.485 g, 5.860 mmol) and IPy_2BF_4 (2.4 g, 6.450 mmol) in dry dichloromethane (15 mL) at 0°C. Stirring was continued for a further 30 min under argon. The reaction mixture was poured into saturated sodium thiosulfate, the resulting suspension was extracted with dichloromethane (3×25 mL), and the combined organic extracts were washed with water, dried, filtered and concentrated in vacuo. The resulting solid residue was purified by column chromatography (eluant: 1:1 ethyl acetate/hexane) to give iodo derivative **5c** (2.205 g, 99% yield) as a white solid. Mp 76–78°C (methanol). IR (ν, cm^{-1}, NaCl): 3345 (–NH), 1683 (CO). ^1H NMR (δ, ppm): 7.19 (s, 1H, ArH), 6.74 (s, 1H, ArH), 5.12 (bs, 1H, –NH), 4.11 (q, J=7.1 Hz, 2H, $-OCH_2CH_3$), 3.83 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 3.42–3.34 (m, 2H, $-CH_2-$), 2.90–2.84 (m, 2H, $-CH_2-$), 1.22 (t, J=7.1 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 156.35 (CO); 148.97 ($ArOCH_3$); 147.78 ($ArOCH_3$); 133.57 (C); 121.29 (ArH); 112.34 (ArH); 87.77 (C); 60.34 ($-OCH_2CH_3$); 55.78 ($-OCH_3$); 55.55 ($-OCH_3$); 40.66 ($-CH_2-$); 39.96 ($-CH_2-$); 14.39 ($-OCH_2CH_3$). MS (*m*/*z*, %): 379 (M^+, 44), 277 (100). Anal. calcd for $C_{13}H_{18}INO_4$, C 41.18, H 4.78, I 33.47, N 3.69; found, C 40.96, H 4.89, I 33.12, N 3.85.

1.1.3. [2-(4,5-Dimethoxy-2-styrylphenyl)ethyl]carbamic acid ethyl ester (3a). A deoxygenated mixture of iodophenylethylamine derivative **5c** (1 g, 2.635 mmol), styrene (0.605 mL, 5.270 mmol), palladium acetate (59 mg, 0.263 mmol, 10% molar), triphenylphosphine (138 mg, 0.572, 20% molar) and triethylamine (0.441 mL, 3.162 mmol) in dry acetonitrile (14 mL) was heated in a sealed tube at 80°C for 24 h under argon. The suspension was filtered through celite, the filtrate was washed with water (50 mL), dried and concentrated in vacuo. The resulting oily residue was purified by column chromatography (eluant: 99:1 dichloromethane/methanol) to give compound **3a** (571 mg, 70% yield) as an oil. IR (ν, cm^{-1}, NaCl): 3370 (–NH), 1713 (CO). ^1H NMR (δ, ppm): 7.53–7.50 (m, 2H, 2×ArH), 7.37–7.19 (m, 4H, 4×ArH), 7.12 (s, 1H, ArH), 6.90 (d, J=16.0 Hz, 1H, $-CH$=CH–), 6.65 (s, 1H, ArH), 4.94 (m, 1H, –NH), 4.04 (q, J=7.0 Hz, 2H, $-OCH_2CH_3$), 3.91 (s, 3H, $-OCH_3$), 3.85 (s, 3H, $-OCH_3$), 3.37–3.32 (m, 2H, $-CH_2-$), 2.94–2.88 (m, 2H, $-CH_2-$), 1.24 (t, J=7.0 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 155.44 (CO), 148.54 ($ArOCH_3$), 147.58 ($ArOCH_3$), 137.36 (C), 129.35 (C), 128.40 (3×ArH), 128.33 (C), 127.15 (ArH), 126.14 (2×ArH), 125.19 (ArH), 112.72 (ArH), 108.19 (ArH), 60.40 ($-OCH_2CH_3$), 55.67 ($-OCH_3$), 55.61 ($-OCH_3$), 41.91 ($-CH_2-$), 32.87 ($-CH_2-$), 14.34 ($-OCH_2CH_3$). MS (*m*/*z*, %): 355 (M^+, 31), 253 (100). HRMS: $C_{21}H_{25}NO_4$ (M^+), calcd 355.1784; found 355.1782.

Further elution allowed us to isolate compound **7a** (139 mg, 17% yield) as an oil. IR (ν, cm^{-1}, NaCl): 3365 (–NH), 1715 (CO). ^1H NMR (δ, ppm): 7.54–7.51 (m, 2H, 2×ArH), 7.38–7.21 (m, 3H, 3×ArH), 7.00 (s, 1H, ArH), 6.74 (s, 1H, ArH), 5.78 (d, J=1.4 Hz, 1H, C=CH*H*); 5.21 (d, J=1.4 Hz, 1H, C=C*H*H); 4.81 (m, 1H, –NH), 4.09 (q, J=7.0 Hz, 2H, $-OCH_2CH_3$), 3.84 (s, 3H, $-OCH_3$), 3.83 (s, 3H, $-OCH_3$), 3.25–3.16 (m, 2H, $-CH_2-$), 2.91–2.86 (m, 2H, $-CH_2$), 1.24 (t, J=7.0 Hz, 3H, $-OCH_2CH_3$). ^{13}C NMR (δ, ppm): 155.45 (CO), 150.08 (C), 148.61 ($ArOCH_3$), 147.63 ($ArOCH_3$), 137.63 (C), 129.40 (C), 128.76 (3×ArH), 128.44 (C), 127.51 (ArH), 126.20 (ArH), 112.80 (ArH),

108.23 (ArH), 102.96 (=CH_2), 60.41 (–O$CH_2$$CH_3$), 55.68 (–$OCH_3$), 55.63 (–$OCH_3$), 41.47 (–$CH_2$–), 32.89 (–$CH_2$–), 14.33 (–$OCH_2CH_3$). MS (*m/z*, %, FAB): 356 [(M^++H), 100]. HRMS (FAB): $C_{21}H_{26}NO_4$ (M^++H) calcd 356.1784; found 356.1789.

1.1.4. 2,3-Dimethoxyphenanthrene (12). Air was bubbled for 10 min through a stirred solution of stilbene derivative **3a** (105 mg, 0.295 mmol) in diethyl ether (180 mL) and dichloromethane (5 mL). A catalytic amount of iodine (12 mg, 0.03 mmol) was added and the mixture was then irradiated for 5 h in a photochemical reactor equipped with a Pyrex condenser and a Hanovia 450 W medium-pressure Hg vapour lamp. Saturated sodium thiosulfate (100 mL) was added and the organic layer was dried, filtered and concentrated in vacuo. The residue was purified by column chromatography (eluant 4:1 dichloromethane/hexane) to afford phenanthrene **12** (11 mg, 15% yield). Mp 166–168°C (methanol). IR (ν, cm^{-1}, NaCl): 2925 (ArH), 1269 (C–O). ^{1}H NMR (δ, ppm): 8.53 (d, J=8.0 Hz, 1H, ArH), 8.00 (s, 1H, ArH), 7.88–7.85 (m, 1H, ArH), 7.72–7.49 (m, 4H, 4×ArH), 7.25 (s, 1H, ArH), 4.11 (s, 3H, –OCH_3), 4.04 (s, 3H, –OCH_3). ^{13}C NMR (δ, ppm): 149.23 (2×ArOCH_3); 131.29 (C); 129.68 (C); 128.65 (ArH); 127.09 (C); 126.15 (ArH); 125.92 (ArH); 125.52 (ArH); 125.19 (ArH); 124.78 (C); 122.09 (ArH); 108.24 (ArH); 103.16 (ArH); 55.96 (–OCH_3); 55.89 (–OCH_3). MS (*m/z*, %): 238 (M^+, 100). Anal. calcd for $C_{16}H_{14}O_2$, C 80.65, H 5.92; found, C 80.32, H 5.69.

1.1.5. [2-(4,5-Dimethoxy-2-styrylphenyl)ethyl]methylcarbamic acid ethyl ester (3b). A solution of stilbene **3a** (490 mg, 1.379 mmol) in dry THF (6 mL) was added dropwise under argon to a stirred suspension of sodium hydride (290 mg, 12 mmol) in dry THF (6 mL). The stirring was continued at rt for 30 min and methyl iodide (2.92 mL, 46.900 mmol) was added. The resulting mixture was stirred for a further 3 h and diluted with water (20 mL). The THF was removed in vacuo and the remaining aqueous suspension was extracted with dichloromethane (3×20 mL), the combined organic extracts were washed with water (40 mL), dried, filtered and concentrated in vacuo to give *N*-methylcarbamic acid derivative **3b** (510 mg, 100% yield) as an oil. This compound was used directly without further purification. IR (ν, cm^{-1}, NaCl): 1688 (CO). ^{1}H NMR (δ, ppm, 331 K): 7.52–7.49 (m, 2H, 2×ArH), 7.35–7.21 (m, 4H, 4×ArH), 7.12 (s, 1H, ArH), 6.90 (d, J=16.0 Hz, 1H, –CH=CH–), 6.66 (s, 1H, ArH), 4.07 (q, J=7.0 Hz, 2H, –O$CH_2$$CH_3$), 3.89 (s, 3H, –$OCH_3$), 3.86 (s, 3H, –$OCH_3$), 3.45–3.39 (m, 2H, –$CH_2$–), 2.95–2.89 (m, 2H, –$CH_2$–), 2.81 (s, 3H, –$NCH_3$), 1.17 (t, J=7.0 Hz, 3H, –OCH_2CH_3). ^{13}C NMR (δ, ppm, 331 K): 156.14 (CO), 149.15 (ArOCH_3), 148.13 (ArOCH_3), 137.73 (C), 129.89 (C), 128.88 (C), 128.65 (ArH), 128.43 (2×ArH), 127.15 (ArH), 126.22 (2×ArH), 125.62 (ArH), 113.61 (ArH), 109.37 (ArH), 60.88 (–O$CH_2$$CH_3$), 55.01 (–$OCH_3$), 55.91 (–$OCH_3$), 50.43 (–$CH_2$–), 34.71 (–$NCH_3$), 31.83 (–$CH_2$–), 14.56 (–$OCH_2CH_3$). MS (*m/z*, %): 369 ($M^+$, 35), 116 (100). HRMS: $C_{22}H_{27}NO_4$ (M^+) calcd 369.1940; found 369.1943.

1.1.6. 7,8-Dimethoxy-2-methyl-5-styryl-3,4-dihydro-2*H*-isoquinolin-1-one (4b). Triflic anhydride (0.410 mL, 2.436 mmol) was added dropwise over 5 min to a solution of compound **3b** (180 mg, 0.487 mmol) and DMAP (178 mg, 1.461 mmol) in dry dichloromethane (5 mL) at 0°C. The mixture was stirred for 21 h under argon at rt. The reaction mixture was then diluted with dichloromethane (10 mL) and the resulting solution was successively washed with saturated potassium carbonate (20 mL), 10% aq. hydrochloric acid (30 mL) and water (50 mL). The solution was dried, filtered and concentrated in vacuo to give a yellow oil, which was purified by column chromatography (eluant: 95:5 dichloromethane/methanol) to give isoquinolinone **4b** (106 mg, 77% yield) as a colorless oil. IR (ν, cm^{-1}, NaCl): 1639 (CO). ^{1}H NMR (δ, ppm): 7.50 (d, J=8.6 Hz, 1H, ArH), 7.48 (s, 1H, ArH), 7.39–7.16 (m, 5H, 5×ArH), 6.89 (d, J=16.1 Hz, 1H, –CH=CH–), 3.99 (s, 3H, –OCH_3), 3.91 (s, 3H, –OCH_3), 3.47–3.42 (m, 2H, –CH_2–), 3.15 (s, 3H, –NCH_3), 2.96–2.91 (m, 2H, –CH_2–). ^{13}C NMR (δ, ppm): 162.85 (CO), 152.43 (ArOCH_3), 149.59 (ArOCH_3), 136.89 (C), 130.78 (ArH), 129.88 (C), 129.57 (C), 128.53 (2×ArH), 127.68 (ArH), 126.28 (2×ArH), 124.88 (ArH), 124.29 (C), 112.20 (ArH), 61.36 (–OCH_3), 55.97 (–OCH_3), 47.49 (–CH_2–), 34.61 (–NCH_3), 25.39 (–CH_2–). MS (*m/z*, %): 323 (M^+, 64), 294 (100). HRMS: $C_{20}H_{21}NO_3$ (M^+) calcd 323.1521; found 323.1518.

1.1.7. 11,12-Dimethoxy-2-methyl-3,4-dihydro-2*H*-naphtho[2,1-*f*]isoquinolin-1-one (13a). Irradiation of stilbene isoquinolinone **4b** (115 mg, 0.355 mmol) under the same conditions as for the cyclization of **4a** afforded naphthoisoquinolinone **13a** (60 mg, 52% yield). Mp 134–136°C (ethyl acetate). IR (ν, cm^{-1}, NaCl): 1648 (CO). ^{1}H NMR (δ, ppm): 9.70–9.67 (m, 1H, ArH), 7.88–7.79 (m, 2H, 2×ArH), 7.72–7.60 (m, 3H, 3×ArH), 4.16 (s, 3H, –OCH_3), 3.97 (s, 3H, –OCH_3), 3.64–3.59 (m, 2H, –CH_2–), 3.36–3.31 (m, 2H, –CH_2–), 3.23 (s, 3H, –NCH_3). ^{13}C NMR (δ, ppm): 163.01 (CO), 151.89 (ArOCH_3), 157.74 (ArOCH_3), 132.95 (C), 132.89 (C), 129.52 (C), 128.27 (2×ArH), 127.44 (ArH), 127.26 (ArH), 127.06 (ArH), 126.46 (C), 123.49 (C), 121.65 (ArH), 61.93 (–OCH_3), 55.94 (–OCH_3), 47.59 (–CH_2–), 34.84 (–NCH_3), 25.69 (–CH_2–). MS (*m/z*, %): 321 (M^+, 39), 57 (100). Anal. calcd for $C_{20}H_{19}NO_3$, C 74.75, H 5.96, N 4.36; found, C 75.02, H 5.81, N 4.59.

1.1.8. 12-Hydroxy-11-methoxy-2-methyl-3,4-dihydro-2*H*-naphtho[2,1-*f*]isoquinolin-1-one (16a). A 1 M solution of boron trichloride in dichloromethane (0.800 mL, 0.781 mmol) was added dropwise under argon to a stirred solution of isoquinolinone **13a** (25 mg, 0.078 mmol) in dichloromethane (5 mL) and the mixture was stirred for 15 min. Water (5 mL) was added to the reaction mixture and this was stirred for a further 15 min. The product was extracted with dichloromethane (3×10 mL) and the combined organic extracts were washed with water (15 mL), dried, filtered and concentrated in vacuo. The resulting solid residue was purified by column chromatography (eluant: 1:1 ethyl acetate/hexane) to give phenolic naphthoisoquinolinone **16a** (24 mg, 100%) as a yellow solid. Mp 120–122°C (ethyl acetate). IR (ν, cm^{-1}, NaCl): 1647 (CO). ^{1}H NMR (δ, ppm, 500 MHz): 13.05 (s, 1H, –OH), 9.71–9.67 (m, 1H, ArH), 7.81–7.77 (m, 1H, ArH), 7.67 (d, J=9.2 Hz, 1H, ArH), 7.63–7.58 (m, 2H, 2×ArH), 7.52 (d, J=9.2 Hz, 1H, ArH), 3.98 (s, 3H, –OCH_3), 3.63 (t, J=6.9 Hz, 2H, –CH_2–), 3.35 (t, J=6.9 Hz, 2H, –CH_2–), 3.16 (s, 3H, –NCH_3). ^{13}C NMR (δ, ppm, 125.72 MHz): 168.64 (CO), 152.35 (C), 144.61 (C), 133.41 (C), 130.70 (C), 129.34 (C), 128.69

(ArH), 128.12 (ArH), 127.49 (ArH), 126.77 (ArH), 125.48 (ArH), 122.20 (C), 121.66 (ArH), 112.66 (C), 59.34 (−OCH_3), 47.77 (−CH_2−), 34.62 (−NCH_3), 24.06 (−CH_2−). MS (*m*/*z*, %): 307 (M^+, 100), 292 (80), 249 (34). Anal. calcd for $C_{19}H_{17}NO_3$, C 74.25, H 5.58, N 4.56; found, C 73.99, H 5.86, N 4.31.

1.1.9. 11-Methoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinolin-12-ol (annoretine) (1a). Lithium aluminium hydride (12 mg, 0.325 mmol) was added to a stirred solution of naphthoisoquinolinone **16a** (20 mg, 0.065 mmol) in THF (3 mL) at 0°C. The reaction mixture was stirred at rt for 5 h and the excess lithium aluminium hydride was destroyed by consecutive addition of water (0.013 mL), 15% aq. sodium hydroxide (0.13 mL) and water (0.039 mL). The resulting suspension was filtered under vacuum, the solid residue was washed with a 95:5 dichloromethane/methanol mixture, the filtrate was concentrated in vacuo and the solid residue was purified by preparative TLC (eluant: 9:1 dichloromethane/methanol) to give annoretine (**1a**) (12 mg, 63% yield) as a white solid. Mp 160–162°C (MeOH, sublimation). IR (ν, cm^{-1}, NaCl): 3435 (−OH). ^{1}H NMR (δ, ppm): 9.38–9.34 (m, 1H, ArH), 7.87–7.82 (m, 2H, 2×ArH), 7.78–7.55 (m, 3H, 3×ArH), 3.79 (s, 3H, −OCH_3), 3.77 (s, 2H, −CH_2−), 3.27 (t, *J*=5.9 Hz, 2H, −CH_2−), 2.85 (t, *J*=5.9 Hz, 2H, −CH_2−), 2.57 (s, 3H, −NCH_3). ^{13}C NMR (δ, ppm): 144.73 (C), 141.47 (C), 132.37 (C), 128.91 (C), 128.19 (ArH), 127.15 (C), 127.00 (ArH), 126.63 (ArH), 126.17 (ArH), 125.42 (C), 124.94 (ArH), 123.15 (C), 121.89 (ArH), 121.85 (C), 60.08 (−OCH_3), 53.04 (−CH_2−), 52.48 (−CH_2−), 45.92 (−NCH_3), 26.76 (−CH_2−). MS (*m*/*z*, %): 293 (M^+, 97), 250 (100). Anal. calcd for $C_{19}H_{19}NO_2$, C 77.79, H 6.53, N 4.77; found, C 78.11, H 6.32, N 4.93.

1.1.10. 3-Isopropoxy-4-methoxybenzaldehyde (6c). Potassium carbonate (12.717 mg, 92.014 mmol) was added to a solution of isovanillin (**6b**) in dry DMF (100 mL) and to this mixture was added 2-bromopropane (15.12 mL, 161.024 mmol). The reaction mixture was stirred for 48 h at rt and then poured into water (100 mL). The resulting suspension was extracted with diethyl ether (3×100 mL), the combined organic extracts were washed with water (4×150 mL), dried, filtered and concentrated in vacuo to give compound **6c** (8.869 g, 99% yield) as a yellow oil, which was used without further purification. IR (ν, cm^{-1}, NaCl): 1689 (−CHO). ^{1}H NMR (δ, ppm): 9.84 (s, 1H, −CHO), 7.47 (d, *J*=7.9 Hz, 1H, ArH), 7.42 (s, 1H, ArH), 6.98 (d, *J*=7.9 Hz, 1H, ArH), 4.64 (m, *J*=6.1 Hz, 1H, −CH−), 3.94 (s, 3H, −OCH_3), 1.39 (d, *J*=6.1 Hz, 6H, 2×−CH_3). ^{13}C NMR (δ, ppm): 190.28 (CHO), 155.09 (C), 147.25 (C), 129.49 (C), 125.88 (ArH), 112.18 (ArH), 110.48 (ArH), 70.67 (−CH−), 55.49 (−OCH_3), 21.35 (2x−CH_3). MS (*m*/*z*, %): 194 (M^+, 16), 151 (100). HRMS: $C_{11}H_{14}O_3$ (M^+) calcd 194.0943; found 194.0944.

1.1.11. 2-Isopropoxy-1-methoxy-4-vinylbenzene (6d). A 1.6 M solution of *n*-BuLi in hexane (27 mL) was added under argon to a stirred suspension of methyltriphenylphosphonium bromide (14.72 g, 41.190 mmol) in dry THF (70 mL) at −78°C (dry ice/acetone bath). The mixture was allowed to warm up to rt, stirred for 20 min, cooled again to −78°C, and a solution of benzaldehyde **6c** (4 g, 20.595 mmol) in dry THF (20 mL) was added dropwise. The resulting mixture was stirred for 4 h at rt. The solvent was removed in vacuo, the residue was suspended in water (100 mL) and the suspension was extracted with dichloromethane (3×70 mL). The combined organic extracts were washed with a 1:2 methanol/water mixture, dried, filtered and concentrated in vacuo. The resulting solid residue was purified by column chromatography (eluant: 1:9 ethyl acetate/hexane) to give styrene **6d** (3.69 g, 93% yield) as a yellow oil, which was used without further purification. IR (ν, cm^{-1}, NaCl): 1510 (C−O), 1261 (C−O). ^{1}H NMR (δ, ppm): 6.99 (d, *J*=2.2 Hz, 1H, ArH), 6.93 (dd, *J*=8.5, 1.5 Hz, 1H, ArH), 6.78 (dd, *J*=8.5, 1.5 Hz, 1H, ArH), 6.61 (dd, *J*=17.6, 10.9 Hz, 1H, −C*H*═CHH), 5.58 (dd, *J*=17.6, 0.9 Hz, 1H, −CH═CH*H*), 5.11 (d, *J*=10.9 Hz, 1H, −CH═C*H*H), 4.52 (m, *J*=6.1 Hz, 1H, −CH−), 3.79 (s, 3H, −OCH_3), 1.35 (d, *J*=6.1 Hz, 6H, 2×−CH_3). ^{13}C NMR (δ, ppm): 150.20 (C), 146.94 (C), 136.22 (ArH), 130.36 (C), 119.56 (ArH), 113.29 (ArH), 111.49 (ArH), 111.35 (−CH═*CH_2*), 71.18 (−CH−), 55.59 (−OCH_3), 21.82 (2×−CH_3). MS (*m*/*z*, %): 192 (M^+, 22), 135 (100). HRMS: $C_{12}H_{16}O_2$ (M^+) calcd 192.1150; found 192.1146.

1.1.12. (2-{2-[2-(3-Isopropoxy-4-methoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)carbamic acid ethyl ester (3c). Compound **3c** was prepared in 55% yield from compound **5c** (1.2 g, 3.165 mmol) and styrene **6d** (730 mg, 3.797 mmol) following the same procedure as for compound **3a**. Mp 121–122°C (methanol). IR (ν, cm^{-1}, NaCl): 3421 (−NH), 1676 (CO). ^{1}H NMR (δ, ppm): 7.28–7.07 (m, 4H, ArH), 6.88 (s, 1H, ArH), 6.83 (d, *J*=7.5 Hz, 1H, ArH), 6.56 (s, 1H, ArH), 4.87 (bs, 1H, −NH), 4.69 (m, *J*=5.9 Hz, 1H, −CH−), 4.07 (q, *J*=6.9 Hz, 2H, −O*CH_2*CH_3), 3.93 (s, 3H, −OCH_3), 3.87 (s, 3H, −OCH_3), 3.86 (s, 3H, −OCH_3), 3.36 (t, *J*=6.8 Hz, 2H, −CH_2−), 2.93 (t, *J*=6.8 Hz, 2H, −CH_2−), 1.41 (d, *J*=5.9 Hz, 6H, 2×−CH_3), 1.18 (t, *J*=6.9 Hz, 3H, −OCH_2*CH_3*). ^{13}C NMR (δ, ppm): 156.52 (CO), 150.06 (C), 148.31 (C), 147.65 (C), 147.15 (C), 130.58 (C), 128.91 (C), 128.81 (C), 128.32 (ArH), 123.31 (ArH), 119.85 (ArH), 113.62 (ArH), 112.79 (ArH), 111.74 (ArH), 108.14 (ArH), 71.25 (−CH−), 60.51 (−O*CH_2*CH_3), 55.79 (−OCH_3), 55.76 (−OCH_3), 55.73 (−OCH_3), 42.05 (−CH_2−), 33.20 (−CH_2−), 21.94 (2×−CH_3), 14.44 (−OCH_2*CH_3*). MS (*m*/*z*, %): 443 (M^+, 100). Anal. calcd for $C_{25}H_{33}NO_6$, C 67.70, H 7.50, N 3.16; found, C 67.56, H 7.69, N 3.12.

Proceeding as for **7a**, compound **7b** was isolated in a 17% yield, as an oil. IR (ν, cm^{-1}, NaCl): 3410 (−NH), 1690 (CO). ^{1}H NMR (δ, ppm): 7.28–7.10 (m, 2H, 2×ArH), 6.86 (s, 1H, ArH), 6.82–6.76 (m, 2H, 2×ArH)5.67 (d, *J*=1.1 Hz, 1H, −C═C*H*H), 5.10 (d, *J*=1.1 Hz, 1H, −C═CH*H*), 4.87 (bs, 1H, −NH), 4.46 (h, *J*=6.1 Hz, 1H, −CH−), 4.07 (q, *J*=6.9 Hz, 2H, O*CH_2*CH_3), 3.90 (s, 3H, −OCH_3), 3.86 (s, 3H, −OCH_3), 3.84 (s, 3H, −OCH_3), 3.21 (t, *J*=6.8 Hz, 2H, −CH_2−), 2.53 (t, *J*=6.8 Hz, 2H, −CH_2−),1.32 (d, *J*=6.1 Hz, 6H, 2×CH_3), 1.18 (t, *J*=6.9 Hz, 3H, −OCH_2*CH_3*). ^{13}C NMR (δ, ppm): 156.51 (CO), 150.62 (C), 149.48 (C), 148.33 (C), 147.68 (C), 147.17 (C), 130.61 (C), 129.01 (C), 128.47 (C), 119.89 (ArH), 113.60 (ArH), 112.78 (ArH), 111.66 (ArH), 108.05 (ArH), 103.11 (═CH_2), 71.26 (−CH−), 60.48 (−O*CH_2*CH_3), 55.81 (−OCH_3), 55.78 (−OCH_3),

55.74 (−OCH_3), 42.08 (−CH_2−), 33.23 (−CH_2−), 21.93 (2×−CH_3), 14.41 (−OCH_2CH_3). MS (*m*/*z*, %, FAB): 444 [(M^++H), 100]. HRMS (FAB): $C_{25}H_{34}NO_6$ (M^++H) calcd 444.2308; found 444.2313.

1.1.13. (2-{2-[2-(3-Isopropoxy-4-methoxyphenyl)vinyl]-4,5-dimethoxyphenyl}ethyl)methylcarbamic acid ethyl ester (3d). Treatment of stilbene **3c** (705 mg, 1.1589 mmol) with sodium hydride (480 mg, 19.868 mmol) and methyl iodide (3.46 mL, 55.635 mmol) under the same conditions as for the methylation of **3a** provided a solid residue that was purified by column chromatography (eluant: 99:1 dichloromethane/methanol) to give stilbene derivative **3d** (712 mg, 98% yield) as a white solid. Mp 113–115°C (methanol). IR (ν, cm^{-1}, NaCl): 1695 (CO). ^{1}H NMR (δ, ppm, 331 K): 7.18–7.05 (m, 4H, ArH), 6.86 (d, *J*=8.5 Hz, 1H, ArH), 6.82 (d, *J*=15.7 Hz, 1H, −C*H*=CH−), 6.66 (s, 1H, ArH), 4.60 (m, *J*=5.9 Hz, 1H, −CH−), 4.09 (q, *J*=6.9 Hz, 2H, −O$CH_2$$CH_3$), 3.91 (s, 3H, −$OCH_3$), 3.87 (s, 3H, −$OCH_3$), 3.85 (s, 3H, −$OCH_3$), 3.43 (t, *J*=7.5 Hz, 2H, −CH_2−), 2.93 (t, *J*=7.5 Hz, 2H, −CH_2−), 2.83 (s, 3H, −NCH_3), 1.37 (d, *J*=5.9 Hz, 6H, 2×−CH_3), 1.20 (t, *J*=6.9 Hz, 3H, −OCH_2CH_3). ^{13}C NMR (δ, ppm, 331 K): 156.33 (CO), 150.80 (C), 149.00 (C), 148.25 (C), 147.81 (C), 131.24 (C), 129.64 (C), 129.33 (C), 128.66 (ArH), 123.91 (ArH), 120.24 (ArH), 115.09 (ArH), 113.75 (ArH), 112.83 (ArH), 109.39 (ArH), 71.97 (−CH−), 61.03 (−O$CH_2$$CH_3$), 56.17 (2×−$OCH_3$), 56.08 (−$OCH_3$), 50.61 (−$CH_2$−), 34.84 (−$NCH_3$), 31.47 (−$CH_2$−), 22.17 (2×−$CH_3$), 14.62 (−$OCH_2CH_3$). MS (*m*/*z*, %): 457 (M^+, 100). Anal. calcd for $C_{26}H_{35}NO_6$, C 68.25, H 7.71, N 3.06; found, C 67.89, H 7.78, N 2.89.

1.1.14. 5-[2-(3-Isopropoxy-4-methoxyphenyl)vinyl]-7,8-dimethoxy-2-methyl-3,4-dihydro-2*H*-isoquinolin-1-one (4c). Naphthoisoquinolinone **4c** was prepared in 87% yield from stilbene derivative **3d** (410 mg, 0.896 mmol) following the same procedure as for its analogue **4b**. Mp 59–62°C (methanol). IR (ν, cm^{-1}, NaCl): 1653 (CO). ^{1}H NMR (δ, ppm): 7.19 (s, 1H, ArH), 7.09–7.06 (m, 2H, ArH), 7.04 (d, *J*=16.0 Hz, 1H, −C*H*=CH−), 6.88 (d, *J*=8.8 Hz, 1H, ArH), 6.83 (d, *J*=16.0 Hz, 1H, −CH=C*H*−), 4.59 (m, *J*=5.9 Hz, 1H, −CH−), 4.11 (q,*J*=6.9 Hz, 2H, −O$CH_2$$CH_3$), 3.99 (s, 3H, −$OCH_3$), 3.92 (s, 3H, −$OCH_3$), 3.88 (s, 3H, −$OCH_3$), 3.49–3.44 (m, 2H, −$CH_2$−), 3.17 (s, 3H, −$NCH_3$), 2.98–2.93 (m, 2H, −$CH_2$−), 1.40 (d, *J*=5.9 Hz, 6H, 2×−CH_3), 1.25 (t, *J*=6.9 Hz, 3H, −OCH_2CH_3). ^{13}C NMR (δ, ppm): 163.01 (CO), 152.46 (C), 150.58 (C), 149.33 (C), 147.19 (C), 130.69 (ArH), 130.24 (C), 130.02 (C), 129.32 (C), 124.32 (C), 123.04 (ArH), 120.08 (ArH), 114.16 (ArH), 112.12 (ArH), 111.86 (ArH), 71.59 (−CH−), 61.43 (−OCH_3), 56.01 (−OCH_3), 55.84 (−OCH_3), 47.60 (−CH_2−), 34.70 (−NCH_3), 25.49 (−CH_2−), 21.99 (2×−H_3). MS (*m*/*z*, %): 411 (M^+, 100). Anal. calcd for $C_{24}H_{29}NO_5$, C 70.05, H 7.10, N 3.40; found, C 69.76, H 7.22, N 3.71.

1.1.15. 8-Isopropoxy-9,11,12-trimethoxy-2-methyl-3,4-dihydro-2*H*-naphtho[2,1-*f*]isoquinolin-1-one (13b). Irradiation of stilbene isoquinolinone **4c** (110 mg, 0.267 mmol) under the same conditions as for the cyclization of **4b** afforded 41% yield of the corresponding naphthoisoquinolinone **13b**. Mp 160–162°C (methanol). IR (ν, cm^{-1}, NaCl): 1653 (CO). ^{1}H NMR (δ, ppm): 9.26 (s, 1H, ArH), 7.71 (d, *J*=9.1 Hz, 1H, ArH), 7.60 (d, *J*=9.1 Hz, 1H, ArH), 7.23 (s, 1H, ArH), 4.80 (m, *J*=5.9 Hz, 1H, −CH−), 4.16 (s, 3H, −OCH_3), 4.09 (s, 3H, −OCH_3), 3.98 (s, 3H, −OCH_3), 3.63–3.58 (m, 2H, −CH_2−), 3.34–3.28 (m, 2H, −CH_2−), 3.22 (s, 3H, −NCH_3), 1.50 (d, *J*=5.9 Hz, 6H, 2×−CH_3). ^{13}C NMR (δ, ppm): 163.08 (CO), 151.12 (C), 150.87 (C), 149.76 (C), 147.63 (C), 133.09 (C), 128.56 (C), 126.38 (ArH+C), 125.71 (C), 123.78 (C), 122.45 (C), 119.88 (ArH), 110.56 (ArH), 109.22 (ArH), 70.64 (−CH−), 61.84 (−OCH_3), 59.93 (−OCH_3), 55.80 (−OCH_3), 47.45 (−CH_2−), 34.68 (−NCH_3), 25.56 (−CH_2−), 21.85 (2×−CH_3). MS (*m*/*z*, %): 409 (M^+, 100). Anal. calcd for $C_{24}H_{27}NO_5$, C 70.40, H 6.65, N 3.42; found, C 70.63, H 6.47, N 3.24.

1.1.16. 8,12-Dihydroxy-9,11-dimethoxy-2-methyl-3,4-dihydro-2*H*-naphtho[2,1-*f*]isoquinolin-1-one (16b). Naphthoisoquinolinone **13b** (45 mg, 0.109 mmol) was reacted with boron trichloride (1.1 mL of a 1 M solution in dichloromethane) following the same conditions as for compound **13a** to give diphenolic naphthoisoquinolinone **16b** in 77% yield. Mp 232–234°C (methanol). IR (ν, cm^{-1}, NaCl): 3450 (−OH), 1617 (CO). ^{1}H NMR (δ, ppm, 500 MHz, DMSO): 13.25 (s, 1H, −OH), 9.73 (s, 1H, −OH), 9.11 (s, 1H, ArH), 7.70 (d, *J*=9.1 Hz, 1H, ArH), 7.47 (d, *J*=9.1 Hz, 1H, ArH), 7.22 (s, 1H, ArH), 3.95 (s, 3H, −OCH_3), 3.94 (s, 3H, −OCH_3), 3.70–3.67 (m, 2H, −CH_2−), 3.38–3.36 (m, 2H, −CH_2−), 3.09 (s, 3H, −NCH_3). ^{13}C NMR (δ, ppm, 125.72 MHz, DMSO): 167.97 (CO), 150.96 (C), 147.77 (C), 147.47 (C), 142.24 (C), 131.88 (C), 129.09 (C), 126.94 (C), 124.13 (ArH), 121.84 (C), 120.99 (C), 120.35 (ArH), 111.74 (ArH), 111.22 (C), 109.11 (ArH), 58.82 (−OCH_3), 55.24 (−OCH_3), 46.95 (−CH_2−), 34.04 (−NCH_3), 23.27 (−CH_2−). MS (*m*/*z*, %): 353 (M^+, 71), 338 (100). Anal. calcd for $C_{20}H_{19}NO_5$, C 67.98, H 5.42, N 3.96; found, C 68.13, H 5.19, N 4.07.

1.1.17. 9,11-Dimethoxy-2-methyl-1,2,3,4-tetrahydronaphtho[2,1-*f*]isoquinoline-8,12-diol (litebamine) (1b). Reduction of naphthoisoquinolinone **16b** (11 mg, 0.031 mmol) with lithium aluminium hydride (12 mg, 1.550 mmol) under the same conditions as for **1a** provided 57% yield of litebamine (**1b**) as a white solid. Mp 133–136°C (methanol). IR (ν, cm^{-1}, NaCl): 3434 (−OH). ^{1}H NMR (δ, ppm, 500 MHz, DMSO): 9.51 (s, 1H, −OH), 9.24 (s, 1H, −OH), 8.93 (s, 1H, ArH), 7.62 (d, *J*=9.0 Hz, 1H, ArH), 7.45 (d, *J*=9.0 Hz, 1H, ArH), 7.20 (s, 1H, ArH), 3.94 (s, 3H, −OCH_3), 3.72 (s, 3H, −OCH_3), 3.58 (s, 2H, −CH_2−), 3.11–3.09 (m, 2H, −CH_2−), 2.75–2.73 (m, 2H, −CH_2−), 2.44 (s, 3H, −NCH_3). ^{13}C NMR (δ, ppm, 125.72 MHz, DMSO): 147.81 (C), 146.26 (C), 144.87 (C), 140.99 (C), 127.81 (C), 126.43 (C), 123.44 (C), 123.28 (ArH), 123.02 (C), 122.16 (C), 121.61 (C), 119.76 (ArH), 111.47 (ArH), 107.84 (ArH), 59.59 (−OCH_3), 55.19 (−OCH_3), 53.07 (−CH_2−), 51.98 (−CH_2−), 45.60 (−NCH_3), 26.26 (−CH_2−). MS (*m*/*z*, %): 339 (M^+, 63), 63 (100). Anal. calcd for $C_{20}H_{21}NO_4$, C 70.78, H 6.24, N 4.13; found, C 70.83, H 6.02, N 4.37.

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17. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 166420 (**1a**, solvent: MeOH). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk]. Crystallographic data for annoretine (**1a**). $C_{19}H_{19}NO_2$, M=293.35, T=293(2) K. Triclinic, space group $P\bar{1}$ with a=11.5575(17), b=12.0696(16), c=13.271(3) Å, α=112.933(13)°, β=111.403(14)°, γ=97.794(14)°, U=1501.7(4) Å^3, D_c (Z=4)=1.298 g cm^{-3}. F(000)=624, μ(Cu Kα)=6.66 cm^{-1}; 6453 unique data ($2\theta_{max}$=150°), 6177 with $I>2\sigma(I)$, conventional $R1[I>2\sigma(I)]$=0.0413, $wR2$ [all data]=0.1323, GOF [all data]=1.017. Data were obtained on an Enraf-Nonius CAD4-Mach3 diffractometer (graphite crystal monochromator, λ=1.5418 Å) using the ω=2θ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the non-hydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-93) using all data; $wR^2=[(\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.
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20. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 166421 (**1b**, solvent: MeOH). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk]. Crystallographic data for litebamine (**1b**). $C_{20}H_{21}NO_4$, M=339.38, T=293(2) K. Triclinic, space group $P\bar{1}$ with a=23.264(8), b=7.392(2), c=10.152(3) Å, α=90°, β=114.975(7)°, γ=90°, U=1582.7(9) Å^3, D_c (Z=4)=1.424 g cm^{-3}. F(000)=720, μ(Mo Kα)=0.099 cm^{-1}; 1725 unique data ($2\theta_{max}$=150°), 1233 with $I>2\sigma(I)$, conventional $R1[I>2\sigma(I)]$=0.0656, $wR2$ [all data]=0.1426, GOF [all data]=0.968. Data were obtained on a SMART Bruker diffractometer (graphite crystal monochromator, λ=0.71073 Å) using the ω=2θ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the non-hydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-97) using all data; $wR^2=[(\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.
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